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Crystal structures of hexakis-(2,6-di-*O*-methyl)-cyclomaltohexaose (dimethyl-α-cyclodextrin) crystallized from acetone, and crystallized from hot water [1,2]

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Abstract

X-ray diffraction studies were carried out on hexakis-(2,6-di-*O*-methyl)-cyclomaltohexaose (dimethyl-α-cyclodextrin, DIMEA) crystallized at room temperature from solutions in pure acetone as the 1:1 inclusion complex, and crystallized from aqueous solution at 80 °C without water of hydration. In both crystal structures, the DIMEA molecules adopt a round shape stabilized by systematic intramolecular O-3–H ··· O-2 hydrogen bonds between neighbouring glucose units, and the DIMEA-cavities are closed at the O-6–Me rims by methoxy groups forming van der Waals contacts across the molecular opening. In the DIMEA–acetone complex, the guest molecule is fully included and exhibits excessive thermal motions. In anhydrous DIMEA, the remaining cavity volume is occupied by a methoxy group of a neighbouring DIMEA molecule. © 1996 Elsevier Science Ltd.

Keywords: Crystal structure; Dimethyl-α-cyclodextrin; Acetone; Hydrogen bonding

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[1] *Topography of Cyclodextrin Inclusion Complexes*, Part 40. For Part 39, see ref. [4]. For part 38, see ref. [13].

[2] Data have been deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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1. Introduction

The crystallization properties of methylated cyclodextrins (cyclomaltooligosaccharides, CDs) are highly peculiar. Since the temperature coefficients of their solubilities in water are negative [1], crystals can be grown by heating aqueous solutions. Crystal structures of methylated cyclodextrins grown from hot water have been reported by several groups of authors: heptakis-(2,3,6-tri-*O*-methyl)-β-CD (TRIMEB) [2], heptakis-(2,6-di-*O*-methyl)-β-CD (DIMEB) [3], hexakis-(2,3,6-tri-*O*-methyl)-α-CD (TRIMEA) [4], and hexakis-(2,6-di-*O*-methyl)-α-CD (DIMEA) [5]. As common features, these crystal structures contain no (DIMEB, TRIMEA, DIMEA) or only one (TRIMEB) molecule of crystal water per CD, the CD cavities are free of water, and the molecules are found in bowl-shaped conformation, i.e. the cavity is closed at the O-6 end by suitably oriented O-6–CH_3 methoxy groups. At room temperature (RT), methylated CDs can be crystallized from salt solutions. From dilute NaCl solutions, anhydrous TRIMEA crystallizes at RT isomorphously as from hot water [4]. DIMEA crystallizes from dilute NaCl solution at RT as a monohydrate and exhibits a different crystal packing as the anhydrous DIMEA obtained from hot water [5].

To extend and systematize these studies, we determined the crystal structure of DIMEA grown from a solution in pure acetone at room temperature. In addition, and independent of the work of Harata [5], we performed a study on DIMEA grown from hot water.

2. Experimental

Crystallization.—(A) DIMEA–acetone. DIMEA dissolves well in pure acetone. By slow evaporation at room temperature, needle-shaped crystals of the 1:1 inclusion complex DIMEA–acetone are obtained. The diffraction quality is poorer than for typical crystals of native cyclodextrins; this is the normal situation for crystals of methylated CDs and their inclusion complexes.

(B) DIMEA grown from hot water. Compared to TRIMEB [2], DIMEB [3] and TRIMEA [4], DIMEA is more difficult to crystallize from hot water. Whereas slow evaporation of dilute TRIMEA solutions kept at 40 °C yields excellent crystals [4], dilute DIMEA solutions evaporated at temperatures < 70 °C produce only glassy material. For dilute DIMEA solutions, the water temperature has to be increased to 80 °C to obtain crystals. At this temperature, the solutions exhibit extensive convection that can be observed by the naked eye. The prismatic crystals always show poor diffraction quality, with high mosaicity and a diffraction pattern extending only to a crystallographic resolution of $\lambda/2\sin\theta = 1.0$ Å.

X-ray diffraction experiments.—X-ray diffraction data were collected at room temperature on crystals glued to glass pins (Enraf-Nonius Turbo-CAD4 diffractometer on a FR571 rotating anode generator operating with 45 kV/80 mA, Ni-filtered CuK_α radiation with $\lambda = 1.542$ Å). For both crystals, unit cell dimensions were determined from the diffraction angles of 25 reflections. Relevant crystallographic data is given in Table 1.

Table 1
Crystallographic data

	DIMEA–acetone	Anhydrous DIMEA
Crystal habitus	transparent needle	transparent plate
Crystal size (mm^3)	$0.90 \times 0.09 \times 0.07$	$0.20 \times 0.15 \times 0.07$
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a (Å)	14.172(11)	15.239(3)
b (Å)	10.707(2)	17.089(5)
c (Å)	21.267(11)	22.848(5)
β (°)	106.12(5)	
Vol (Å^3)	3100(3)	5950(3)
Z	2	4
Vol Z^{-1} (Å^3)	1550(1)	1487.5(8)
D_{calc} (g cm^{-1})	1.285	1.274
μ (mm^{-1})	0.908	0.907
Scan mode	ω-scan	ω-scan
Measured reflections	5357	3420
$R_{merge}(F^2)$	0.060	—
Unique reflections	4871	3420
Unique refl. $F^2 > 2\sigma(F^2)$	3355	1677
$\lambda/2\sin\theta_{max}$ (Å)	0.89	1.01
Absorption correction	ψ-scan method	none
$\omega R(F^2)$ (for $F^2 > 2\sigma(F^2)$)	0.196	0.176
R (for $F^2 > 2\sigma(F^2)$)	0.076	0.081

Structure solution and refinement.—(A) DIMEA–acetone. As is indicated by the close similarity of the unit cell constants, the crystalline complex DIMEA–acetone is isomorphous with the crystal structures of DIMEA–monohydrate [5], DIMEA–1-propanol and DIMEA–iodine [6]. Therefore, atomic coordinates of DIMEA–1-propanol were used for initial phasing (all O-6 and Me groups, and the guest molecule omitted). During anisotropic refinement against F^2, the missing atoms could be located from difference Fourier maps (program SHELXL93 [7] aided by computer graphics, program FRODO [8]). One methyl group of DIMEA, C-8^3, is disordered over two approximately half-occupied positions. Due to extensive thermal vibrations, the acetone guest molecule had to be refined with constrained ideal covalent geometry. Hydrogen atoms bonded to C were included in the model in their ideal positions ('riding model' [7]). The hydroxyl H-atoms could not be located in difference Fourier maps. Attempts to include these H-atoms using search and generation options of the refinement program resulted in unrealistic hydrogen bond geometries; therefore, they are not included in the final model. No difference electron density peaks were found close to O-3 atoms which might indicate partially O-3-methylated material.

(B) DIMEA grown from hot water. The structure solution was severely hampered by the limited quality of the diffraction data. Finally, the cyclodextrin skeleton (without O-6 and Me groups) of DIMEA–acetone was successfully used as a structural model for Patterson search methods (program PATSEE [9]), which yielded a model suitable for

rough initial phasing. The completion of the model and structure refinement was performed as for DIMEA–acetone. Hydroxyl H-atoms could not be located. No water site showed up in difference Fourier maps. To establish whether possible weakly occupied water sites were overlooked, the program PLATON [10] was used to search the crystal structure for voids large enough to accommodate water molecules. No such voids were found, showing that DIMEA crystallizes from hot water without any water of hydration molecules.

3. Results and discussion

General.—Fractional atomic coordinates and equivalent isotropic temperature factors of DIMEA–acetone and of anhydrous DIMEA are listed in Tables 2 and 3, respectively. Atom labelling is the same as in our previous contributions ([3,4] and references therein), e.g. C-2^3 means atom C-2 of glucose residue 3 of the oligosaccharide. The methyl C-atoms attached to O-2^n and O-6^n are labelled C-7^n and C-8^n, respectively. The crystal structure of anhydrous DIMEA is very similar as the one determined by Harata [5], however with variations in a great number of details (see below).

Crystal packing.—In the crystalline DIMEA–acetone complex, the molecules are arranged in a herringbone packing, Fig. 1A, which is analogous to the herringbone packing frequently observed for crystalline inclusion complexes of native β-CD (e.g. refs. [11–13]). In this cage-type packing mode, the CD-cavity is closed by the rims of neighbouring CD-molecules. In contrast to the herringbone packing of complexes of native β-CD, however, which contain interstitial voids that are filled with five co-crystallized water molecules, the crystal packing of DIMEA–acetone is tight due to favourable orientation of the methoxy groups. The acetone guest molecule is fully included in the molecular cage with its O-atom oriented towards the O-6 side of the DIMEA-cavity (see below).

In anhydrous DIMEA, the molecules are arranged in a different packing, Fig. 1B. The primary methoxy group O-6^1–Me intrudes deeply into the cavity of a neighbouring molecule (‘self inclusion’). The primary and secondary methoxy groups are oriented such that interstitial voids are effectively prevented. This crystal packing parallels that of anhydrous TRIMEA [4], which forms the same packing mode, exhibits self-inclusion of a primary methoxy group, and avoids interstitial voids by suitable orientation of the methoxy groups.

Molecular conformation.—The DIMEA molecule is shown for DIMEA–acetone in Fig. 2A, and for anhydrous DIMEA in Fig. 2B in projections on the equatorial planes. A selection of relevant geometrical parameters is given in Tables 4 and 5. The overall conformation is similar for both crystal structures. The molecules adopt round shapes stabilized by a ring of intramolecular hydrogen bonds O-3^n–H ··· O-2^{n-1} (O-3^n ··· O-2^{n-1} hydrogen bond distances in Table 4). In addition, there are systematic weak C-6^n–H ··· O-5^{n-1} interactions [2–4,14,15]. Both molecules have quasi-twofold symmetry with opposing glucoses tilted at similar angles with respect to the molecular axis (Table 4). These tilt angles range from 7.0 to 21.6° in DIMEA–acetone, which is a span of 14.6°, and in anhydrous DIMEA from −3.8 to 23.3°, span = 27.1°. This shows that the complexed molecule is more regularly shaped (compare the flexible molecule in anhydrous TRIMEA, range of tilt angles -4.0 to 38.3°, span = 42.3° [4]). All glucoses are in the normal $^4C_1$ chair conformation with only minor distortions from ideal geometry.

The geometry of the O-4 hexagon (Fig. 3) also reflects the slightly more regular shape of complexed compared to anhydrous DIMEA. The difference between the shortest and the longest diagonal is 0.33 Å for DIMEA–acetone, and 0.46 Å for anhydrous DIMEA, and the largest difference between the angles O-4^{n-1} ··· O-4^{n} ··· O-4^{n+1} is 4.6° for DIMEA–acetone and 8.8° for anhydrous DIMEA.

The most important feature is that both molecules close their molecular cavity at the O-6–Me side by orienting primary methoxy groups towards the cavity axis, so that the terminal methyl groups form van der Waals contacts across the cavity opening. In DIMEA–acetone, this involves two O-6–Me groups, Fig. 2A, and in anhydrous DIMEA three, Fig. 2B. As can be seen with space-filling models, Fig. 4A and B, the O-6–Me ends of the DIMEA-cavities are thereby completely closed. This results in the overall shape of a bowl. Bowl-shaped conformations were observed in all previous crystal structures of methylated cyclodextrins grown from hot water. Bowl shaped conformation of the host is also observed in the inclusion complexes of DIMEA with the small guest molecules water [5], 1-propanol and iodine [6], whereas upon inclusion of the larger molecule 3-iodopropionic acid [18], the O-6 side of the cavity is opened so that the cavity is sufficiently large to accommodate the guest.

Inclusion geometry in DIMEA–acetone.—Although the covalent geometry of the guest molecule had to be constrained in structure refinement, the O and C-atoms could be unambiguously distinguished in Fourier analysis. Therefore, a defined orientation of the guest molecule can be given. The acetone molecule is placed with the C=O bond roughly coincident with the DIMEA molecular axis and its molecular plane oriented along the longest diagonal of the DIMEA O-4 hexagon (Fig. 1A, Fig. 2B). Thermal vibrations of the acetone molecule are excessive, with displacement parameters U_{eq} of the methyl groups ~ 0.45 Å^2 corresponding to rms-displacements of ~ 0.67 Å around the centres of gravity. In view of these large-amplitude vibrations, the discussion about the 'bonding situation' of the guest molecule in terms of short contacts with the host molecule appears to be questionable. Although there might be some very weak host–guest C–H ··· O interactions (O-Ac ··· C-8^{3}A = 3.65(5) Å; C-1(Ac) ··· O-4^1 = 3.83(5) Å; C-2(Ac) ··· O-4^4 = 3.32(5) Å), the general impression is that the guest molecule is oscillating more or less freely within the sterically accessible cavity volume.

It is notable that in the isomorphous complex DIMEA–monohydrate [5], a single water molecule occupies the same space as the much larger acetone molecule in the present complex. In consequence, that water molecule is sterically poorly confined and disordered over four positions.

Comparison of anhydrous DIMEA with the work of Harata [5].—Two crystal structures are available for anhydrous DIMEA, which have been independently determined. They were performed on crystals prepared in a very similar way, and were refined with comparable accuracy. It is of interest to see to which degree these structures actually are the same.

The general features of both crystal structures are identical, with the exception that

Table 2
Fractional atomic coordinates and equivalent isotropic temperature factors U_{eq} of DIMEA–acetone

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
C-1^1	0.4194(6)	0.0128(9)	0.2881(4)	0.084(2)
C-2^1	0.4314(6)	−0.1259(9)	0.2957(5)	0.086(2)
C-3^1	0.3477(6)	−0.1763(10)	0.3185(5)	0.089(2)
C-4^1	0.3410(6)	−0.1098(10)	0.3801(4)	0.082(2)
C-5^1	0.3328(6)	0.0276(9)	0.3705(4)	0.084(2)
C-6^1	0.3357(7)	0.1057(13)	0.4306(5)	0.108(3)
C-7^1	0.4750(7)	−0.2916(11)	0.2318(6)	0.106(3)
C-8^1	0.418(2)	0.144(3)	0.5392(8)	0.229(11)
O-2^1	0.4335(4)	−0.1715(7)	0.2331(3)	0.098(2)
O-3^1	0.3627(6)	−0.3095(8)	0.3321(4)	0.127(3)
O-4^1	0.2522(3)	−0.1591(6)	0.3914(2)	0.083(2)
O-5^1	0.4172(4)	0.0697(7)	0.3480(3)	0.095(2)
O-6^1	0.4139(6)	0.0670(11)	0.4817(4)	0.140(3)
C-1^2	0.1983(6)	0.2644(9)	0.0862(5)	0.084(2)
C-2^2	0.2612(6)	0.1629(10)	0.0710(5)	0.088(3)
C-3^2	0.2870(6)	0.0691(8)	0.1256(4)	0.079(2)
C-4^2	0.3286(6)	0.1319(8)	0.1906(4)	0.078(2)
C-5^2	0.2653(6)	0.2397(9)	0.2000(4)	0.081(2)
C-6^2	0.3107(7)	0.3166(11)	0.2607(5)	0.100(3)
C-7^2	0.2598(10)	0.1025(14)	−0.0370(6)	0.127(4)
C-8^2	0.4562(11)	0.415(2)	0.3230(8)	0.156(6)
O-2^2	0.2102(5)	0.1048(7)	0.0104(3)	0.103(2)
O-3^2	0.3553(5)	−0.0230(7)	0.1141(3)	0.108(2)
O-4^2	0.3312(4)	0.0374(6)	0.2387(3)	0.084(2)
O-5^2	0.2466(4)	0.3232(6)	0.1453(3)	0.092(2)
O-6^2	0.4069(6)	0.3494(8)	0.2643(5)	0.133(3)
C-1^3	−0.1919(6)	0.2579(9)	0.0340(4)	0.080(2)
C-2^3	−0.1453(7)	0.2177(10)	−0.0182(4)	0.091(3)
C-3^3	−0.0421(6)	0.1747(11)	0.0107(4)	0.091(3)
C-4^3	0.0182(6)	0.2715(10)	0.0578(4)	0.084(2)
C-5^3	−0.0347(5)	0.3064(9)	0.1095(4)	0.077(2)
C-6^3	0.0145(7)	0.4128(11)	0.1526(5)	0.097(3)
C-7^3	−0.2371(13)	0.136(2)	−0.1227(5)	0.148(5)
C-8^{3}A [a]	−0.002(4)	0.340(4)	0.253(2)	0.22(3)
C-8^{3}B [a]	0.007(3)	0.529(3)	0.244(2)	0.25(3)
O-2^3	−0.2039(5)	0.1209(9)	−0.0545(3)	0.114(2)
O-3^3	0.0033(5)	0.1493(10)	−0.0400(3)	0.123(3)
O-4^3	0.1088(4)	0.2100(6)	0.0898(3)	0.084(2)
O-5^3	−0.1317(4)	0.3502(6)	0.0749(3)	0.087(2)
O-6^3	−0.0320(7)	0.4285(13)	0.2014(5)	0.172(5)
C-1^4	−0.3686(5)	−0.0081(9)	0.1764(4)	0.073(2)
C-2^4	−0.3929(6)	−0.0500(10)	0.1053(4)	0.083(2)
C-3^4	−0.3114(6)	−0.0055(8)	0.0769(3)	0.071(2)
C-4^4	−0.2938(5)	0.1303(9)	0.0863(4)	0.074(2)
C-5^4	−0.2859(5)	0.1772(8)	0.1561(4)	0.076(2)
C-6^4	−0.2929(7)	0.3151(9)	0.1618(4)	0.090(2)
C-7^4	−0.4831(7)	−0.2263(12)	0.0527(5)	0.110(3)
C-8^4	−0.4579(9)	0.392(2)	0.1378(7)	0.143(5)

Table 2 (continued)

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
O-2^4	−0.4030(4)	−0.1818(6)	0.1033(3)	0.088(2)
O-3^4	−0.3346(5)	−0.0367(7)	0.0086(3)	0.097(2)
O-4^4	−0.2026(4)	0.1534(6)	0.0712(2)	0.079(1)
O-5^4	−0.3632(4)	0.1223(6)	0.1794(3)	0.082(2)
O-6^4	−0.3766(5)	0.3672(7)	0.1144(3)	0.105(2)
C-1^5	−0.1385(5)	−0.2091(9)	0.3926(4)	0.075(2)
C-2^5	−0.2040(6)	−0.2978(8)	0.3440(4)	0.076(2)
C-3^5	−0.2273(6)	−0.2428(8)	0.2769(4)	0.076(2)
C-4^5	−0.2700(5)	−0.1142(8)	0.2745(4)	0.073(2)
C-5^5	−0.2027(6)	−0.0291(8)	0.3266(4)	0.069(2)
C-6^5	−0.2406(6)	0.0956(9)	0.3348(4)	0.081(2)
C-7^5	−0.2125(8)	−0.5207(10)	0.3488(7)	0.116(4)
C-8^5	−0.3716(7)	0.2045(10)	0.3554(6)	0.105(3)
O-2^5	−0.1548(4)	−0.4148(6)	0.3489(3)	0.100(2)
O-3^5	−0.2946(4)	−0.3242(6)	0.2317(3)	0.095(2)
O-4^5	−0.2792(3)	−0.0644(6)	0.2107(2)	0.074(1)
O-5^5	−0.1831(4)	−0.0918(6)	0.3905(2)	0.077(1)
O-6^5	−0.3328(4)	0.0869(7)	0.3479(3)	0.097(2)
C-1^6	0.2499(6)	−0.1884(10)	0.4553(4)	0.086(2)
C-2^6	0.2034(6)	−0.3189(11)	0.4532(5)	0.093(3)
C-3^6	0.1000(6)	−0.3155(9)	0.4101(4)	0.083(2)
C-4^6	0.0422(5)	−0.2067(9)	0.4290(4)	0.075(2)
C-5^6	0.0963(6)	−0.0854(9)	0.4347(4)	0.078(2)
C-6^6	0.0492(7)	0.0167(11)	0.4648(5)	0.097(3)
C-7^6	0.293(2)	−0.510(2)	0.4690(12)	0.204(9)
C-8^6	0.0595(12)	0.201(2)	0.4043(9)	0.147(5)
O-2^6	0.2616(5)	−0.4046(8)	0.4294(4)	0.115(2)
O-3^6	0.0535(5)	−0.4314(7)	0.4131(3)	0.098(2)
O-4^6	−0.0478(3)	−0.1997(6)	0.3776(2)	0.076(1)
O-5^6	0.1947(4)	−0.1007(7)	0.4778(3)	0.091(2)
O-6^6	0.0926(5)	0.1357(8)	0.4633(4)	0.114(2)
O-Ac	0.040(3)	0.004(3)	0.2437(12)	0.41(2)
C-1(Ac)	0.022(2)	−0.085(3)	0.2080(10)	0.29(1)
C-2(Ac)	0.073(5)	−0.208(4)	0.225(2)	0.47(3)
C-3(Ac)	−0.055(3)	−0.0797(6)	0. 1432(14)	0.44(2)

[a] Occupancies of sites C-8^{3}A and C-8^{3}B are 0.44 and 0.56, respectively.

Harata noted two-fold disorder of one O-6–Me group, which is not observed in the present structure. Significant differences in the unit cell constants, however, suggest that there might be further structural variations (Harata: $a = 15.195(2)$, $b = 17.012(1)$, $c = 22.481(2)$ Å). Since Harata used a different glucose numbering, and different definitions of some geometrical parameters, the geometrical analysis was repeated on the published coordinates [5] after appropriate re-numbering of the glucose residues ($n = n_{\mathrm{Harata}} - 1$). The results obtained for some characteristic parameters are given in Table 6.

Table 6 shows that the DIMEA molecule in [5] is somewhat more distorted than in the present work: the intramolecular O-2 ··· O-3′ hydrogen bond distances, the diagonals of the O-4 hexagon, the O-4^n ··· O-4^{n+1} ··· O-4^{n+2} angles and the glucose tilt

Table 3
Fractional atomic coordinates and equivalent isotropic temperature factors U_{eq} of anhydrous DIMEA crystallized from hot water

Atom	*x/a*	*y/b*	*z/c*	U_{eq} (Å^2)
C-1^1	0.2491(13)	0.1659(11)	0.1244(9)	0.110(6)
C-2^1	0.3135(13)	0.1078(11)	0.1054(8)	0.109(6)
C-3^1	0.3353(12)	0.1252(11)	0.0418(8)	0.112(6)
C-4^1	0.2525(11)	0.1294(10)	0.0048(7)	0.102(6)
C-5^1	0.1856(12)	0.1846(10)	0.0311(7)	0.106(6)
C-6^1	0.0918(14)	0.1895(13)	0.0040(9)	0.143(7)
C-7^1	0.441(2)	0.0484(13)	0.1458(10)	0.18(1)
C-8^1	−0.036(2)	0.113(2)	−0.0105(14)	0.28(2)
O-2^1	0.3893(10)	0.1176(7)	0.1410(5)	0.129(4)
O-3^1	0.3925(10)	0.0638(7)	0.0198(5)	0.145(5)
O-4^1	0.2823(8)	0.1636(6)	−0.0487(4)	0.112(4)
O-5^1	0.1706(8)	0.1662(7)	0.0922(4)	0.116(4)
O-6^1	0.623(12)	0.1126(9)	−0.0004(6)	0.168(6)
C-1^2	0.3371(12)	0.4462(10)	0.2139(8)	0.097(5)
C-2^2	0.3647(12)	0.3695(10)	0.2419(8)	0.099(6)
C-3^2	0.3661(11)	0.3026(10)	0.2008(7)	0.099(5)
C-4^2	0.2767(11)	0.2981(9)	0.1679(7)	0.094(5)
C-5^2	0.2493(11)	0.3775(9)	0.1433(8)	0.095(5)
C-6^2	0.1562(14)	0.3760(13)	0.1193(9)	0.139(8)
C-7^2	0.4628(14)	0.3605(12)	0.3240(8)	0.143(8)
C-8^2	0.113(4)	0.420(3)	0.035(2)	0.43(4)
O-2^2	0.4502(8)	0.3805(7)	0.2653(5)	0.119(4)
O-3^2	0.3785(8)	0.2294(6)	0.2311(4)	0.114(4)
O-4^2	0.2846(7)	0.2435(6)	0.1204(4)	0.096(3)
O-5^2	0.2513(8)	0.4366(7)	0.1893(4)	0.106(3)
O-6^2	0.1449(14)	0.4398(13)	0.0817(11)	0.24(1)
C-1^3	0.5255(13)	0.6515(11)	0.0928(8)	0.105(6)
C-2^3	0.5714(13)	0.6093(11)	0.1425(8)	0.116(6)
C-3^3	0.5338(12)	0.5322(10)	0.1557(8)	0.112(6)
C-4^3	0.4339(11)	0.5424(10)	0.1665(7)	0.097(5)
C-5^3	0.3875(11)	0.5908(10)	0.1202(7)	0.095(5)
C-6^3	0.2948(13)	0.6114(12)	0.1350(9)	0.129(7)
C-7^3	0.719(2)	0.635(3)	0.149(2)	0.46(4)
C-8^3	0.168(2)	0.643(2)	0.084(2)	0.22(2)
O-2^3	0.6601(9)	0.5981(8)	0.1233(5)	0.133(5)
O-3^3	0.5752(9)	0.4940(9)	0.2063(5)	0.150(5)
O-4^3	0.3995(7)	0.4646(6)	0.1705(4)	0.095(3)
O-5^3	0.4344(8)	0.6631(6)	0.1098(4)	0.107(4)
O-6^3	0.2543(12)	0.6408(11)	0.0815(8)	0.194(8)
C-1^4	0.5473(12)	0.6180(12)	−0.1336(8)	0.107(6)
C-2^4	0.6346(12)	0.6186(10)	−0.1024(7)	0.101(5)
C-3^4	0.6224(11)	0.5918(10)	−0.0394(7)	0.094(5)
C-4^4	0.5526(11)	0.6460(10)	−0.0116(7)	0.092(5)
C-5^4	0.4716(12)	0.6555(10)	−0.0480(8)	0.107(6)
C-6^4	0.4124(13)	0.7195(11)	−0.0261(8)	0.125(7)
C-7^4	0.753(2)	0.6060(14)	−0.1712(11)	0.19(1)
C-8^4	0.420(2)	0.852(2)	0.0130(12)	0.24(2)

Table 3 (continued)

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
O-2^4	0.6962(9)	0.5689(7)	−0.1305(6)	0.122(4)
O-3^4	0.7015(7)	0.5962(8)	−0.0065(5)	0.131(4)
O-4^4	0.5301(7)	0.6064(5)	0.0424(4)	0.096(3)
O-5^4	0.4899(8)	0.6706(6)	−0.1087(4)	0.109(4)
O-6^4	0.4626(11)	0.7892(9)	−0.0188(7)	0.170(6)
C-1^5	0.3878(14)	0.3651(12)	−0.2232(9)	0.120(6)
C-2^5	0.4836(13)	0.3791(11)	−0.2398(8)	0.115(6)
C-3^5	0.5295(13)	0.4300(11)	−0.1914(8)	0.112(6)
C-4^5	0.4783(11)	0.5039(10)	−0.1814(8)	0.100(5)
C-5^5	0.3790(13)	0.4847(11)	−0.1693(9)	0.121(6)
C-6^5	0.326(2)	0.5577(13)	−0.1645(9)	0.144(8)
C-7^5	0.582(2)	0.2945(14)	−0.2913(9)	0.20(1)
C-8^5	0.232(2)	0.542(2)	−0.0831(10)	0.22(2)
O-2^5	0.5250(10)	0.3030(8)	−0.2431(6)	0.144(5)
O-3^5	0.6161(8)	0.4475(7)	−0.2088(4)	0.116(4)
O-4^5	0.5139(7)	0.5411(6)	−0.1300(4)	0.093(3)
O-5^5	0.3441(8)	0.4378(8)	−0.2167(5)	0.119(4)
O-6^5	0.2386(10)	0.5433(10)	−0.1447(8)	0.174(6)
C-1^6	0.2478(14)	0.1351(12)	−0.1021(9)	0.121(6)
C-2^6	0.3243(13)	0.1141(13)	−0.1404(9)	0.128(7)
C-3^6	0.3811(13)	0.1841(10)	−0.1555(8)	0.115(6)
C-4^6	0.3262(12)	0.2511(11)	−0.1746(8)	0.110(6)
C-5^6	0.2454(12)	0.2677(10)	−0.1379(8)	0.109(6)
C-6^6	0.1813(14)	0.3264(12)	−0.1609(9)	0.135(7)
C-7^6	0.411(2)	−0.0025(13)	−0.1408(11)	0.22(1)
C-8^6	0.096(2)	0.261(2)	−0.2353(11)	0.20(1)
O-2^6	0.3750(11)	0.0545(8)	−0.1100(5)	0.151(5)
O-3^6	0.4467(9)	0.1676(8)	−0.1981(6)	0.152(5)
O-4^6	0.3805(9)	0.3203(7)	−0.1737(4)	0.113(4)
O-5^6	0.1991(8)	0.1944(7)	−0.1298(5)	0.118(4)
O-6^6	0.1634(9)	0.3191(10)	−0.2219(6)	0.160(6)

angles span significantly wider ranges. The methoxy groups are oriented in a similar but not identical way, with variations in the C-1–C-2–O-2–C-7 and C-5–C-6–O-6–C-8 torsion angles by up to 8°. These variations are substantially larger than would be expected from refinement inaccuracy alone, indicating that the two crystals investigated actually differed in fine details. This shows that structural details in DIMEA crystals may vary between individual specimens. The differences concern disorder phenomena, subtilities in the molecular conformation and in hydrogen bond interactions. This is in line with observations on β-CD complexes, where significant differences were observed even between different crystals from the same laboratory [19,20]. When interpreting cyclodextrin crystal structures, or those of similar or greater complexity, one must therefore be aware that the numerical details are valid only for the individual crystal on which the structure was determined.

Summary.—DIMEA can be crystallized from solutions in pure acetone, yielding the 1:1 inclusion complex. The DIMEA molecule is bowl-shaped with the cavity closed at

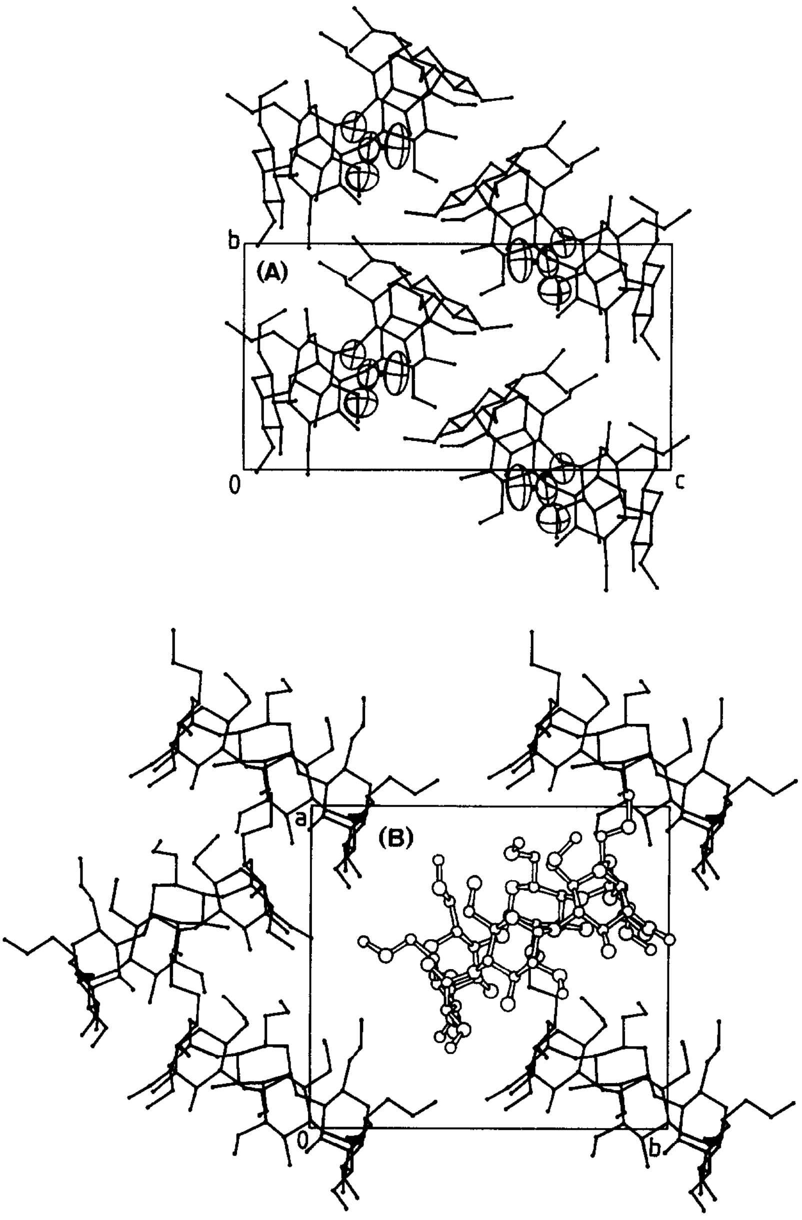

Fig. 1. Crystal packing schemes. (A) DIMEA–acetone, projection is along the *a*-axis. Guest molecules are drawn with displacement ellipsoids (30%-probability level). (B) Anhydrous DIMEA, projection is along the *c*-axis. For clarity, one molecule is drawn with open bonds.

the O-6 side by O-6–Me groups. This way, the cavity volume is reduced approximately to the size of the small guest molecule. Interstitial cavities are avoided by suitable orientation of methoxy groups. The guest molecule exhibits extensive thermal vibra-

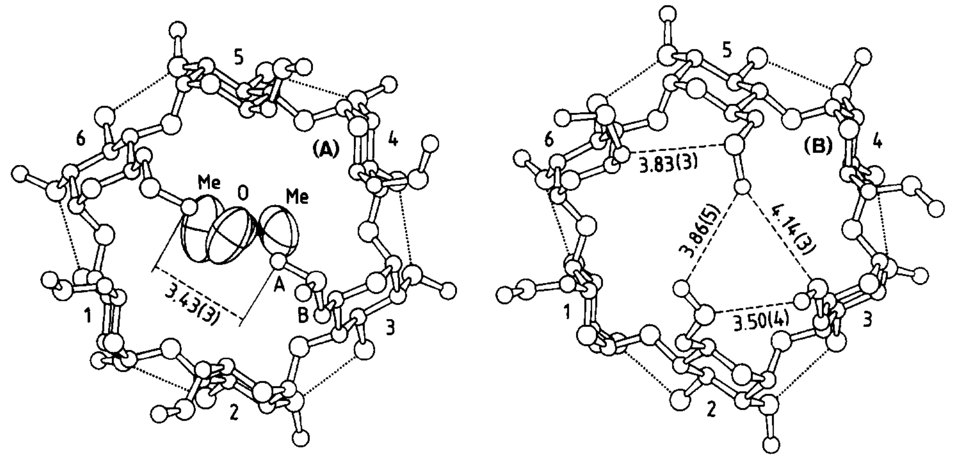

Fig. 2. The DIMEA molecule seen along the molecular axis; the O-6–Me rim is towards the viewer. Dashed lines show van der Waals contacts between O-6–Me groups (distances in Å), dotted lines show intramolecular O-3–H · · · O-2 hydrogen bonds. (A) DIMEA–acetone; to demonstrate the excessive thermal motions of the guest molecule, displacement ellipsoids are drawn at the 30% probability level. The acetone O-atom is oriented towards the viewer. (B) Anhydrous DIMEA grown from 80 °C water.

Table 4
Geometric parameters of the DIMEA molecules

Residue	1	2	3	4	5	6
DIMEA–acetone						
Tilt angle (deg.) [a]	+7.0(2)	+10.5(2)	+21.6(2)	+10.3(2)	+11.4(2)	+21.4(2)
O-2 · · · O-3′ (Å)	2.93(1)	2.87(1)	3.08(1)	3.13(1)	2.89(1)	3.00(1)
C-6 · · · O-5^{n-1} (Å)	3.32(1)	3.34(1)	3.47(1)	3.34(1)	3.29(1)	3.43(1)
H-6 · · · O-5^{n-1} (Å) [b]	2.53	2.58	2.54	2.46	2.48	2.47
C-4–O-4–C-1″ (deg.)	119.8(6)	120.2(6)	118.9(7)	120.6(6)	118.8(5)	119.9(5)
QT (Å) [c]	0.58	0.55	0.57	0.54	0.56	0.56
θ_2 (deg.) [d]	2.4	5.4	4.9	11.0	2.0	6.0
Anhydrous DIMEA						
Tilt angle (deg.) [a]	−3.8(3)	+23.3(3)	+12.2(3)	+4.5(3)	+18.9(3)	+16.2(3)
O-2 · · · O-3′ (Å)	2.81(2)	3.04(2)	3.03(2)	3.00(2)	2.80(2)	2.98(2)
C-6 · · · O-5^{n-1} (Å)	3.47(3)	3.65(3)	3.30(2)	3.27(2)	3.40(3)	3.38(2)
H-6 · · · O-5^{n-1} (Å) [b]	2.65	2.68	2.28	2.39	2.43	2.71
C-4–O-4–C-1″ (deg.)	119(1)	121(1)	120(1)	117(1)	120(1)	119(1)
QT (Å) [c]	0.55	0.56	0.55	0.55	0.58	0.53
θ_2 (deg.) [d]	3.5	6.2	7.4	10.8	3.1	9.9

[a] Tilt angle of the least-squares-(lsq)-plane through C-1–C-2–C-3–C-4–C-5–O-5 with respect to the molecular axis. The molecular axis is defined as the normal to the lsq-plane through the O-4 atoms. Positive and negative signs denote tilt of the O-6 side towards and away from the molecular axis, respectively.

[b] For ideal H-positions with C–H = 1.09 Å; these are well defined by the C-5–C-6–O-6 fragment.

[c] Puckering amplitude [16].

[d] θ_2 measures the deviation from ideal chair conformation [16] (ideal value: $\theta_2 = 0°$).

Table 5
Selection of torsion angles (deg.)

Residue	1	2	3	4	5	6
DIMEA–acetone						
Methoxy groups						
C-1–C-2–O-2–C-7	160.3(7)	124(1)	126(1)	137.5(7)	136.6(9)	127(1)
O-5–C-5–C-6–O-6	−72(1)	−73(1)	69(1)	−71.7(9)	−65.8(8)	68(1)
C-5–C-6–O-6–C-8A	179(1)	−176(1)	79(3)	99(1)	−179.5(8)	82(1)
C-5–C-6–O-6–C-8B			180(2)			
Interglucose linkage						
C-3–C-4–O-4–C-1′	139.1(8)	127.2(7)	123.2(8)	137.6(7)	132.1(1)	123.0(7)
C-4–O-4–C-1′–O-5′	107.0(8)	101.4(8)	103.9(9)	106.4(7)	101.3(8)	103.6(8)
Anhydrous DIMEA						
Methoxy groups						
C-1–C-2–O-2–C-7	155(2)	128(2)	112(3)	95(2)	138(2)	142(2)
O-5–C-5–C-6–O-6	−74(2)	78(2)	70(2)	−74(2)	68(2)	−79(2)
C-5–C-6–O-6–C-8	165(2)	131(4)	164(3)	−168(2)	86(3)	84(2)
Interglucose linkage						
C-3–C-4–O-4–C-1′	141(2)	103(2)	138(1)	134(1)	122(2)	125(2)
C-4–O-4–C-1′–O-5′	115(2)	102(2)	107(2)	106(2)	105(2)	110(2)

tions; this is an example where C–H · · · O interactions are not strong enough to stabilize the guest in a well defined position, although this was principally possible [12,13].

The structural features that were observed for TRIMEB, TRIMEA and DIMEB crystallized from hot water are also observed for DIMEA crystallized under these conditions: the CD molecules adopt a conformation with the cavity closed at the O-6,

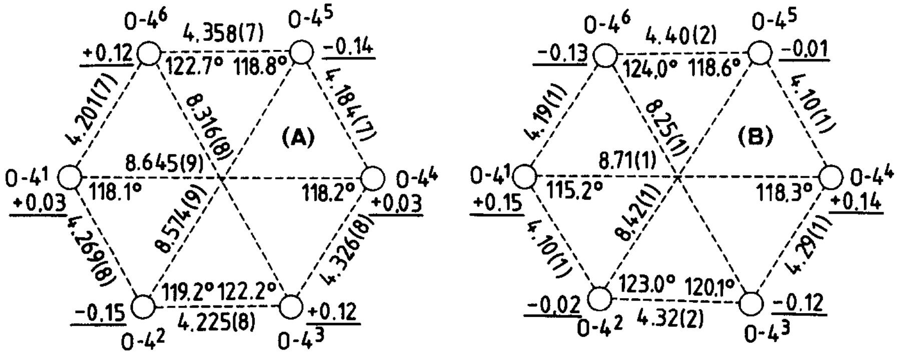

Fig. 3. Geometry of the hexagon of O-4 atoms (given in Å and degrees). Values for angles $O\text{-}4^{n-1} \cdots O\text{-}4^{n} \cdots O\text{-}4^{n+1}$ and deviations from the O-4 least-squares plane are given at the O-4 atoms. (A) DIMEA–acetone. (B) Anhydrous DIMEA grown from 80 °C water.

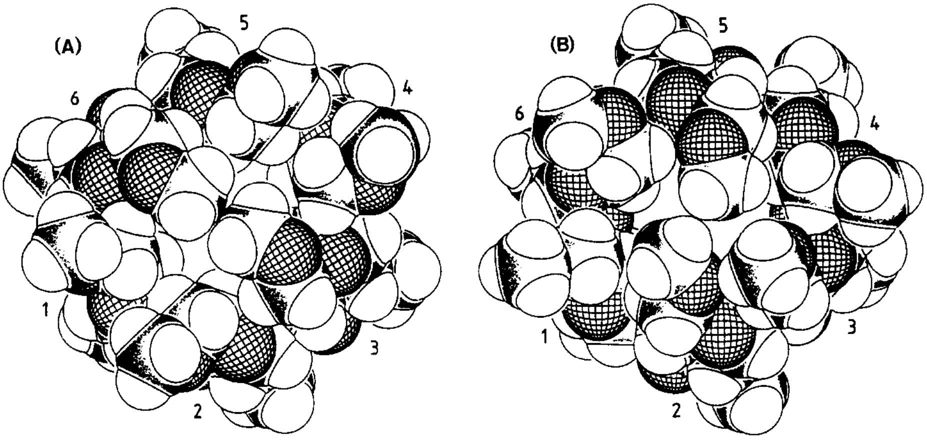

Fig. 4. Space filling models showing that the molecular cavities are closed at the O-6–Me side (program PLUTON [17]). (A) DIMEA–acetone with omitted guest molecule. (B) Anhydrous DIMEA grown from 80 °C water.

and the remaining cavity volume is occupied by a methoxy group of a neighbouring molecule ('self-inclusion'). As for DIMEA–acetone, interstitial cavities are avoided by suitable orientation of methoxy groups. Because, in this situation, no crystal water molecules are needed as space-fillers, the methylated cyclodextrins can crystallize anhydrously (or as TRIMEB [2] with only one water molecule per CD).

Comparison of two independent crystal structures of anhydrous DIMEA (present structure and work in ref. [5]) shows significant variations. This affects details of disorder, molecular conformation and hydrogen bonding.

Table 6
Comparison of the crystal structure of anhydrous DIMEA with the work of Harata [5]

Parameter	Range (this work)	Range (Harata)	Mean $\lvert\Delta x\rvert$ [a]	Max. $\lvert\Delta x\rvert$ [a]
O-2 · · · O-3′ (Å)	2.80–3.04	2.77–3.09	0.034	0.07
O-4 diagonal (Å)	8.25–8.71	8.15–8.71	0.048	0.10
O-4^{n} · · · O-4^{n+1} (Å)	4.10–4.40	4.08–4.37	0.024	0.05
O-4^{n} · · · O-4^{n+1} · · · O-4^{n+2} (deg.)	118.3–124.0	117.8–124.9	0.6	0.9
Tilt angle (deg.)	−3.8–23.3	−4.6–24.7	0.7	1.4
C-4–O-4–C-1″ (deg.)	117–121	117–123	1.6	5.0
C-1–C-2–O-2–C-7 (deg.)			3.6	8
O-5–C-5–C-6–O-6 (deg.)			1.2	3
C-5–C-6–O-6–C-8 (deg.)			4.0	8
C-3–C-4–O-4–C-1′ (deg.)	103–141	109–142	3.9	6
C-4–O-4–C-1′–O-5′ (deg.)	104–116	102–115	1.3	3

[a] $\lvert\Delta x\rvert$ = absolute difference of corresponding values in this work and in ref. [5].

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